University of Khartoum
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Postgraduate Medical Studies Board

Graves' Disease Frequency and Clinical Patterns In Khartoum Teaching Hospital January - July 2004

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Contents

Dedication

To my family for so much

To my mother, Suaad

To my sisters, brothers & friends

To the soul of my father

& brother Ali

To my husband & kids

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ABSTRACT

This is a prospective cross sectional descriptive study performed at Khartoum Teaching Hospital clinics in the period from January 2004 to July 2004.

Aims: To diagnose patients with Graves' disease among thyrotoxic patients by detection of TSI in their sera, to assess the frequency of Graves' disease, and to study the clinical patterns of Graves' disease.

Patients & methods: Forty-nine patients with thyrotoxicosis (confirmed by laboratory investigations) were studied. Data was collected using designed questionnaire. TSI in the sera was detected by RIA. Frequency of Graves' disease was determined. Symptoms and signs of the patients with TSI were studied.

Results: Out of Forty-nine patients, thirty-four patients were found to have detectable significant level of TSI. Frequency of Graves' disease amongst the patients was 69.4% . Main symptoms were dislike to hot weather (70%) , palpitation (35%), tremor (24%) infertility (20%), irritability (35%), fatigability (10%).

Main signs were onycholysis (73%), proptosis (64%), tachycardia (44%) diffuse Goiter (30%), palmer erythema and anemia (7%), thyroid acropachy and pretibial myxodema (0%)

Conclusion: Graves' disease is the commonest cause of hyperthyroidism in patients with thyrotoxicosis in K.T.H. Diagnosis of Graves' disease is done by detection of TSI in the patient serum. Dislike to hot weather and palpitation are major symptoms of Graves'. Proptosis is a major sign of Graves'. Onycholysis is common in Graves' disease.

Recommendations: Accurate diagnosis of Graves' disease by high clinical suspicion and TSI detection in the patient serum. More studies for evaluation of radioactive iodine therapy in Sudan in order to extend it's use in management of Graves' disease.

ملخص الأطروحة

هذه دراسة وصفية عن مرض غراف أجريت في مستشفى الخرطوم في الفترة ما بين يناير وحتى يوليو 2004م.

من أهداف الدراسة تشخيص ومعرفة تعدد مرض غراف ضمن مرضى الإنسمام الدرقي ، كذلك دراسة أعراضه وعلاماته السريرية.

في هذه الدراسة تم تشخيص المرض بواسطة الكشف عن وجود الأجسام المضادة للمرض في دماء المرضى وذلك عن طريق الإشعاع المناعي RIA ومن خلال الدراسة وجد ان 69.4% من مرضى الإنسمام الدرقي يعانون من مرض غراف.

أهم أعراض المرض الجحوظ الدرقي ، ارتفاع ضربات القلب وتحلل الأظافر.

وقد أشارت الدراسة لأهمية دراسة أمراض الغدة الدرقية بغرب السودان ، وأوصت بمزيد من الدراسات عن العلاج باليود الإشعاعي في السودان في حالات مرضى الإنسمام الدرقي.

LIST OF FIGURES

LITERATURE REVIEW

Graves' Disease

Background:

Graves' disease, named after Robert J. Grave's, MD, Circa 1830 is an autoimmune disease characterized by hyperthyroidism due to circulating autoantibodies[1].

Thyroid stimulating imrnunoglobulin (TSI) bind to and activate the thyroid stimulating hormone receptor; causing the thyroid gland to grow & the thyroid follicles to increase synthesis of thyroid hormones.

Graves' disease, along with Hashimoto's thyroiditis is classified as autoimmune thyroid disorders[1].

Graves' disease is the most common ca of hyperthyroidism[2] in some patients, Graves' disease represent part of a more extensive autoimmune process called autoimmune polyglandular syndrome[2] which also associated with pernicious anaemia vitiligo , diabetes mellitus type I, autoimmune adrenal insufficiency & systemic lupus erythromatosus[1].

About %7of patients with Grave's disease have vitiligo and %5of patients with Myasthenia Gravis have thyrotoxicosis at the same time[7].

The natural history is one of alternating relapse and remission[2]. The patients are usually hyperthyroidism but may be; or become, hypo- or euthryroid.

Diagnosis requires identification of suppressed TSH level and elevated levels of free thyroxine (FT_4) and/or tri-iodothyronine (T_3) measurement of TSI (thyroid stimulating immunolgiobulins) is of interest but not required for therapeutic evaluation[3].

Pathophysiology:-

Some controversy continues over use of the terms hyperthyroidism and thyrotoxicosis. Some authorities prefer to use the thyrotoxicosis as the clinical condition that includes hyperthyroidism (then defined the increased synthesis and secretion of thyroid hormone) as one cause.

The exact aetiology of Graves disease remains unknown but are likely related to a defect in immune tolerance leading to the development of a specific autoantibodies directed against various thyroid antigens and against proteins with putatively similar antigen sites in other tissues, notably, the subcutaneous tissues and extra- ocular muscles[3].

Yersina enterocolitica as well as E.coli and other Gram negative organisms, contain TSH binding sites[2]. This raises the possibility that the initiating event in the pathogenesis may be an infection with possible molecular mimicry, in a genetically susceptible individual, but the precise initiating mechanism remains unproven[2].

In view of varied manifestation and their differing courses, it's possible that no single factor is responsible for the entire syndrome With respect to hyperthyroidism, the central disorder is a disruption of homeostatic mechanisms that normally adjust hormone secretion to meet the needs of peripheral tissues[6]. This disruption results from the presence in plasma of an abnormal thyroid stimulator first recognized when it was shown the serum of patients with Graves' disease releases radioiodine from prelabeled ginea pig or mouse thyroid [6, 35-51].

In view of its prolong duration of action relative to that of TSH in this bioassay system ,this material was designated the long-acting thyroid stimulator (LATS).

It was the first thyroid stimulating substance other than TSH to be identified and was later shown to be an IgG immunoglobulin [11].

LATS activity in the mouse assay is due to thyroid — stimulating immunoglobulins (TSI) of the IgG class elaborated by lymphocytes of patients with Graves' disease[6].

In Graves' disease B- and T- lymphocytes mediated autoimmunity are known to be directed at well-known thyroid antigens, thyroglobulins, thyroperoxidase, sodium — iodide symporter, and the TSH receptor[1]. However the TSH receptor itself is the primary auto- antigen of Graves' disease and is responsible for the manifestation of Hyperthyroidism [1].

Thyroid stimulating antibodies produced as part of the autoimmune react and bind to TSH receptor mimic the action of TSH [8].

The hyperthyroidism results from the production of IgG antibodies directed against the TSH-receptor on the thyroid follicular cell which stimulates thyroid hormone production and in the majority Goitre formation, these antibodies are termed thyroid stimulating immunoglobulins or TSR-receptor antibodies (TRAb). and can be detected in the serum of most patients with Graves' disease[12].

Under certain circumstances antibodies to the surface of a cell may stimulate rather than destroy .This would seem to be the case in thyrotoxicosis (Gravess' or Basedow's disease).There has long been indirect evidence suggesting a link between autoimmune processes and this disease: thyroid antibodies are detectable in up to %85 of thyrotoxicosis patients and histologically the majority of the glands removed at operation show varying degrees of thyroiditis and local antibody formation in addition to the characteristic acinar cell hyperplasia; thyrotoxicosis is found with undue frequency in the families of Hashimoto patients; there is an association with gastric autoimmunity in that %30have gastric antibodies and up to 10 %pernicious anaemia.The direct link came with the discovery by Adams and Purves of thyroid stimulating activity in the serum of thyrotoxic patients. Using a new bioassay they found that the serum caused a stimulation of the thyroid gland of the recipient animal which was considerably prolonged

relative to the time course of action of the physiological thyroid stimulating hormone (TSH) from the pituitary; it was ultimately shown that this was due to the presence of thyroid stimulating antibodies (TSAb). These antibodies can block the binding of TSH to thyroid membranes and seem to act in the same manner as TSH, probably by stimulating the identical receptors .Both operate through the adenyl cyclase system as indicated by the potentiating effect of theophylline, and both produce similar changes in the ultrastructural morphology in the thyroid cell, but it is one of Nature's 'passive transfer experiments' which links TSAb most directly with the pathogenesis of Graves' disease. When TSAb from a thyrotoxic mother crosses the placenta it is associated with the production of neonatal hyperthyroidism , which resolves after a few weeks as the maternal IgG is catabolized.

There is a good correlation between the titre of TSAb and the severity of hyperthyroidism. Because TSAb act independently of the pituitary-thyroid axis, iodine uptake by the gland is unaffected by administration of thyroxine or tri-iodothyronine, whereas normally this would cause feedback inhibition and suppression of uptake; this forms the basis of an important diagnostic test for thyrotoxicosis [(26)].

There is reason to believe that enlargement of the thyroid in this disorder is due to the action of antibodies, which react with a 'growth' receptor and directly stimulate cell division as distinct from metabolic hyperactivity. In contrast, from patients with primary myxoedema contain antibodies capable of blocking the mitogenic action of TSH, thereby preventing the regeneration of follicles which is a feature of the enlarged Hashimoto. goiter. We see now that there is considerable diversity in the autoinimune response to the thyroid leading to tissue destruction, metabolic stimulation, growth promotion or mitotic inhibition which in

different combinations account for the variety of forms in which autoimmune thyroid disease presents [12].

In Caucasian there is an association of Graves' disease with HLA-B DR and DR and with the inability to secrete the water soluble glucoprotein from the ABO blood group antigen coded for an chromosome 6, 19 respectively[12].

Family studies showed that %50 monozygotic twins are concordant for hyperthyroidism as opposed to %5 of dizygotic twins[12].

A study performed in Sudan 1980 showed absence of HLA-B_8 in %60of patients with Graves' disease and in the same study TSI level was found to have direct relation with the degree of hyperthyroidism[28].

The same study showed that TSI level always correlates well with the absence of control of thyroid by TSH as indcated by TRH TSH test and T_3 suppression test except in patients with autoimmune thyroiditis and some patients with ophthalmic Graves' disease who were found to be under control of TSH despite high level of circulating TSI[28].

Smoking is weakly associated with Graves' disease but strongly linked with the development of ophthalopathy[12].

The pathogenesis of the ophthalmic component is more anigmatic. One proposed mechanism is the development of antibodies against specific antigen in the extraocular muscles.

Methods of visualization of extraocular muscle changes in thyroid-related eye disease were examined by Fell et al. They showed infiltration of the spaces between the entraocular muscle fibre with monocellular amorphous inflammatory cells and an extracellular matrix[12].

Nothing is known about the pathogenesis of the dermopathy[6].

Frequency:

In the US: Graves' disease is the most common cause of hyperthyroidism. A study done in Olmstead country, Minnesota estimated incidence to be approximately 30cases per 100,000person per year[(1)].

Internationally the frequency of Graves disease as a cause of thryotoscicois ranges from approximately %90-60 in different regions of the world[(1)].

In Wickham study in the United Kingdom, the incidence is reported as 200-100cases per 100,000 population per year.

Morbidity & Mortality:

If left untreated, Graves' disease can cause severe thyrotoxicosis. A life threatening thyrotoxcosis crisis can occur.

Long — standing severe thyrotoxicosis leads to severe weight loss with catabolism of bone and muscle.

Cardiac complications and psycho-cognitive complications can cause significant morbidity. Graves disease also is associated with ophthalmopathy and acropachy which can be disabling and can lead to total loss of hand function[(1)].

Thyroid storm is severe hyperthyroidism ,acute mortality was 100%, now with aggressive therapy and early recognition of the syndrome; the mortality rate remains approximately %20[(1)].

Clinical features:

Although Graves' disease most frequently occurs in women in the middle decade (8:1) more than men, it also occurs in elderly and in children[9].

Because Graves' disease is an autoimmune disorder that also affects other organ systems, taking a careful patient history is essential to establishing the diagnosis[11].

Patients usually present with complaints typical of thyrotoxcosis which include Weight loss, sweats, heat intolerance, nervousness, agitation, tiredness muscle weakness, tremor palpitation, shortness of breath [21].

Grave's disease is the most common (%80-70) cause of thyrotoxicosis, other rare causes include:

-toxic thyroid adenoma

-toxic multinodular goiter.

-Subacute thyroditis

-Factitious thyrotoxicosis [14-20].

Thyrotoxicosis usually develops insidiously, and most patients have had the symptoms for at least 6-3months before presentation[14-20].

Almost every system is affected and patients may initially present to various medical specialties for example, to a cardiologist with atrial fibrillation, or to a neurologist with myopathy [14-20].

Patients with Graves' disease have specific clinical manifestation resulting form underlying autoimmune process[10].

The thyrotoxicosis and autoimmune related manifestation can show independent variants in intensity and time course, causing diagnostic difficulties[10].

Frequent complaints in patients with Graves' disease include rapid heart rate, palpitation, nervousness, tremor, less common complaint include sleep disturbance, weight loss, heat intolerance, hyperdefication, inability to work, proximal muscle weakness and easy fatigability with physical activities.

Graves' disease as with other autoimmune disease, affects females more common than males and has a female to male ratio of 1 : 8 -7

Typically, it is a disease of young women, but it may occur at any age. The typical age range 40-20years, affected women are aged 60-0 3years.

Symptoms of ophthalmopathy include proptosis, lid retraction, lacrimation, gritty sensation in the eyes, photophobia, eye pain, diplopia or even visual loss.

In the elderly subjects with thyrotoxicosis the clinical picture is often significantly different, problems such as weight loss and depression or agitation may predominate- so called apathetic thyrotoxicosis, a condition in which more typical symptoms and signs reflecting sympathetic activation such as tremor and hyperactivity are absent

The common signs are goiter which is typically symmetrical, painless, diffusely enlarged gland and a bruit is often audible over the thyroidIn general, the signs and symptoms of Graves' disease are as follows

- General, metabolic:- basal metabolic rate, heat intolerance, increased sweating, restlessness, anxiety, irritability, insomnia, weight loss despite increase or similar appetite, easy fatigability.
- Dermatologic : - Warm, moists, skin, fine hair, onycholysis, vitiligo, alopecia, pretibial myxaedema palmer erthymema.
- Skeletal : increased bone turn over , ostoporosis, acropachy, elevated serum calcium and alkaline phophatase.

• Cardiovascular: tachycardia, decreased systemic vascular resistance, t cardiac output, increased pulse, atrial fibrillation, left ventricular hypertrophy, cardiomyopathy angina pectoris.

• Respiratory, dyspnoea, respiratory muscle weakness.

• Gastorintestinal: Decreased gastrointestinal transit time, hyperdefication with or without diarrhea, elevated transaminases,

• Ophthalmic: - lid lag , lid retraction, proptosis , diplopia, visual loss in severe optic nerve involvement.

Renal: - increased GFR, polyuria, poly dypsia

Endocrine / reproductive:

Irregular menstrual periods, decreased menstrual volume, gynacomastia, impotence increased sex hormone- binding globulin level, decreased free testostenone levels, worsening diabetes control, decreased parathyroid hormone level

Haemolytic: - increased blood volume, normocytic anaemia low normal to slightly depressed total WBC count with relative lymphocytosis and monocytosis low normal to slightly depressed platelets count.

Lipid metabolism: decreased total cholesterol, decreased triglycerides Common physical finding include widening of the palpebral fissure, tachycardia, hand tremors, fine and usually bilateral, proximal muscle weakness, warm velvety skin .Depression, anxiety or signs of pyschosis may be evident.

Hypokalaemic periodic paralysis is noticed to occur in thyrotoxic patient from Asian origin. Attack may resolve interferon beta-S.b and interleukin - 4when used therapeutically may cause Graves' disease

Trauma to the thyroid also has been reported to be associated with Graves' disease This may include surgery of the thyroid gland percutaneous injection of ethanol, and infraction of a thyroid adenoma Physical findings that are unique to Graves' disease include:

Ophthalmpathy, acropachy and pretibial myxoedema phthalmpathy is a hall mark of Graves' disease %30-20of patient with Graves' disease will have clinical evidence of ophthalmospathy Signs of corneal or conjunctional irritation include conjunctional injection and chemosis .A complete ophthalmic examination, including retinal examination and slit lamp examination by ophthalmologists is indicated if the patient is symptomatic.

Pretibial Myxoedema is infiltrative dermopathy, is characterized by non-pitting infiltration by proteinaceous ground substance, usually in the pretibial area. It rarely occurs in the absence of Graves' disease ophtha1mopathy.

The lesion is often pruritic and erythmatous in its early stages and subsequently become browny. like ophthalmopathy, infiltrative dermopathy may appear years before or after hyperthyroidism [pretibial myxaedma the area is tender and itchy. The lesions may also occur in other parts of the body such as the face and are due to infiltration of the mucopolysactharide nd hyaloronic acid. It occurs in %5of patients with Graves' disease. It usually occur after the onset of treatment (30-4) months Thyroid acropachy: refers to finger clubbing associated with periosteal new bone formation occurring in patients with Graves' disease, almost all patients have thyroid associated Ophthalmpathy and thyroid associated dermopathy Sub-clinical thyrotoxicosis.

This is essentially a biochemical diagnosis, the finding of an undetectable, as opposed to low but detectable, serum TSH concentration

being of more pathophisological significance. The most common cause of suppression of TS/H in the general population is exogenous thyroid hormone therapy, typically T Population surveys have shown that approximately one quarter of those prescribed long- term T display reduction in TSH suggestive of mild over treatment (this is deliberate in relatively small number of patients with a history of thyroid cancer. Since T is prescribed to about %5of the over 60's this medication is a common cause of sub-clinical hyperthyroidism.

There is only limited evidence to suggest that sub-clinical hyperthyroidism is associated with significant symptom but there is a growing of body of evidence that low serum TSH is associated with adverse effects partially in heart and bone.

These findings suggest that data showing effects of mild hyperthyroidism on indices of cardiac functions do indeed translate into significant adverse influences, especially in elderly subjects.

Similar adverse effects of subclinical hyperthyroidism on bone may occur of studies examining effects of subclinical hyperthyroidism on bone mineral density have concluded that there are significant reduction in post-menopoausal women, although these studies are mostly confined to subject taking T

Diagnosis of hyperthyroidism:

The diagnosis should be confirmed by measurement of- :

•TSH: usually present in low concentration.

•Free thyroxine in the serum , high concentration

TSH concentration may be normal or increased if the cause of thyrotoxcosis is either a pituitary adenoma secreting thyroid stimulating hormone or resistance to thyroid hormone.

The diagnosis of Graves' disease depends on clinical history and examination.

The thyroid gland might be impalpable in about %30of cases of both Graves' disease and toxic nodular hyperthyroidism. The presence of thyroid autoantibodies %90-80, (to thyroid proxidase TPO and/or thyroglubulin) is suggestive, but not diagnostic Graves' disease. TSH receptor antibodies, are more specific for diagnosis. Such antibodies are usually negative in cases of toxic hyperthyroidism, if antibodies are positive, in the presence of a nodular goiter, both condtions may co-exists.

Radioisotope scanning, using technetium 99 or iodine-125 typically shows a diffuse pattern of uptake in Graves disease.

- Detection of TSI, (thyroid stimulating immunoglobulin) is diagnostic for Graves' disease. Thyroid stimulating autoantibodies gives 100% detection rate in Graves'disease.

- Complete blood count with differential should be obtained as a baseline and with the development of fever or symptoms of infection- Liver function tests should be obtained to monitor for liver toxicity caused by thionamides.

Treatment:

Medical care:

Treatment of Grave's disease involves alleviation of symptoms and correction of the thyrotoxic state

It also aims to prevent the development of deterioration of extra thyroidal manifestation, particularly ophthalmopathy

B —blockers reduces unpleasant symptoms of sympathetic

over-activity, there may also be an effect on metabolism of thyroxine Propranolol (120-240 mg/day) is the most commonly used Beta-blocker, although any could be used 20 once erthyroid state has been reached, the beta —blocker is discontinued.

Antithyroid drugs:

These include

- Thionaniide : which block the synthesis of thyroid hormone.

- Iodine; which destroys the cells making thyroid horomone, iodine, an excess of which reduces the production of thyroid hormone by an unknown mechanism.

Mode of action of thionamide is by inhibiting organification of iodine and by inhibiting the coupling of iodotyrosine to form T4 & T3

Maximum effect is delayed until existing hormone store are exhausted (for week).

Thionamides:

T 1/2, 4 hrs are commonly used. The drugs accumulate in the thyroid gland and may act for 3 0-40 hrs.

Propyithiourcil : differs from other members of the group in that it also inhibits peripheral conversion of T4 to T3

These drugs are used as principal therapy and as adjuvant to radioiodine to control the disease until the radiation achieves its effect, and to prepare patients for surgery.

Clinical improvment is noticeable in about a week. All three drugs give similar results. Side effects include: allergy, lymphadenopathy, leukopenia which may proceed to agranulocytosis (< 1:10,000) or a plastic anaemia (due to idiosyncrasy rather than allergy)

Blood disorders are most common in the first 2 months of treatment.

Carbimazole:

Is given in a dose of 15-40 mg daily, occasionally a larger dose may be required. This dose is continued until the patient becomes euthyroid, usually after 4-8 weeks and the dose is then gradually reduced to a maintenance dose of 5-15 mg. Therapy is usually given for 12 to 18 months. Children may be given carbimazole in an initial dose of 250 microgram /kg three times daily, adjusted according to response, treatment in children should be undertaken by a specialist. Rashes and pruritis are common but they can be treated with antihistamines without discontinuing therapy. Alternatively propyithiouracil may be substituted. All patients should be advised to report any sore throat immediately because of rare complication.

Propyithiouracil :-

Is given in a dose of 200 to 400mg daily in adults and this dose is maintained until the patient becomes euthyroid; the dose may then be gradually reduced to maintenance dose of 50 to 150mg mg daily. Antithyroid drugs only need to be given once daily because of their prolonged effect on the thyroid. Over-treatment can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy, because it can cause fetal goiter h134 A combination of carbimazole, 40 to 60 mg daily with levothyroxine , 50 to 150 micrograms daily, may be used in a blocking —replacment regimen; therapy is usually given for 18 months. The blocking-replacment regimen is not suitable during

Pregnancy:

The drugs cross the plancenta . Propyithiouracil is more safe during pregnancy and lactation.

A major disadvantage of antithyroid drugs is relapse in (50- 70%) of cases in a few months or years.

Radioiodine: -

Is increasingly used as treatment of choice in hyperthyroidism at all ages. It is simple and in no way unpleasant and it carries no immediate mortality, but it is slow and appropriate dose may be difficult to judge It is indicated in Graves' disease with moderate goiter (40-50 g), with no significant eye signs at first presentation. Exacerbant of symptom may occur in the first 2 weeks. It is contraindicated in pregnancy and lactation and with allergy to iodine. Radioactive iodine may cause transit hypothyroidism or hyperthyroidin (Jod Basedow phenomenon)

Surgery:

Indication for thyrodectomy include:

- Allergic reaction to medical treatment:

- Disease refractory to high dose medical treatment.

- Relapsing disease

- Contraindication to treatment with iodine(14-20).

Management of Graves' ophathalmopathy:

Aims:

- relieve symptoms
- suppress the disease process
- restore muscle mobility
- improve cosmotic appearance

Management include:

- Simple Elevation of the head of the bed
    - Diuretics
    - Dark glasses
- Local:
    - Artifical tears
    - Orbital radiotherapy
    - Tape eyes shut at night
- Surgical:
    - Tarsorrhophy
    - Orbital decompression
- Immunomodulation
- Prednisolone and methypredinosolne
- Plasma exchange
- Cyclosporine and azathioprine

Management of Pretibial myxadema:

For milder cases no treatment is required [(1)].

Topical steroid applied under occlusive plastic film for 3-10 weeks have been helpful[(1)].

In severe cases pulse glucocoriticoid therapy may be tried.

For Acropachy:

No therapy has been proven to be effective [(1)].

OBJECTIVES

The main objectives of this study are:

- To diagnose patients with Graves' disease by detection of TSI in their sera.
- To assess exactly the frequency of Graves' disease among thyrotoxic patients.
- To stand upon the main clinical features in patients with Graves' disease.

MATERIALS AND METHODS

This study is an outpatient based prospective one, in which 49 patients were studied. It is carried out in Khartoum Teaching Hospital and its referral clinics in the period of January 2004 — July 2004. Formal acceptance from all patients to be included in the study was taken beforehand with simple explanation about the study.

All of the patients were already diagnosed as thyrotoxic confirmed by laboratory investigations, namely, their thyroid function tests. The patients ho are already on treatment were also included.

The history of their disease was taken comprising personal data and symptomatology. Then clinical examination of the patients was performed.

The last laboratory investigations regarding their thyroid functions were recorded and their blood was then taken for analysis to detect (TSI) in the sera. Results were tabulated. Data obtained was then statistically analyzed using soft SPSS programme.

Lab investigation:

TSI can be detected either by RIA ‘ or by ELISA” Enzyme- linked immunosorbant assay.

The RIA offers high sensitivity specificity, accuracy and precision.’ Basic principle of RIA depends on detection of low concentration of antigenic hormone by determinating the ability of these antigens to be bound by specific antibodies. The assay is established by:

1. Obtaining the component necessary to perform the assay.

2. Allowing the component to interact under proper circumstances.

3. Separating specific component.

4. Measuring those component by radioactive tracer measurement technique.

5. Obtaining measurement of series of known quantities of substance for later comparison to an unknown amount in the patients sample.

All the above mentioned steps were done. Calculation were done using Gamma counter technique.

Tabulated results were then analyzed staftstically using SPSS Programme.

RESULTS

• Out of the 49 patients studied, thirty four patients were found to have the TSI, which means a frequency of 69.4%.

• As to gender distribution, the females dominate “Figure 1”, the percentage being 85% females compared with 15% males.

• The results showed that the peak age group affected is age group 35-44 years “Figure 2”.

• Figure 3 shows the residence distribution, Khartoum town being 41.2%, followed by Omdurman town 35.3% . Other states 8.8%.

• Distribution of patients by tribes “Figure 4”, showed that most of the patients are of the western Sudanese tribes 52.9% followed by Northern tribes 29.4%, the smallest percentages were those from Eastern and Southern tribes.

• Socioeconomic state of the patients was also studied “Figure 5”, which showed 52.9% were of low state compared with only 2.9% of high socioeconomic state.

Figure1
Gender Distribution in patients with Graves' Disease

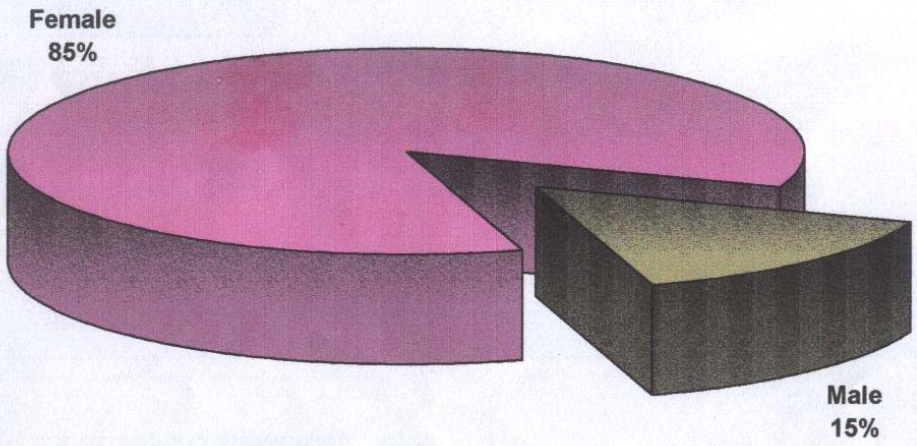


Figure2

Age groups Distribution in patients with Graves' Disease

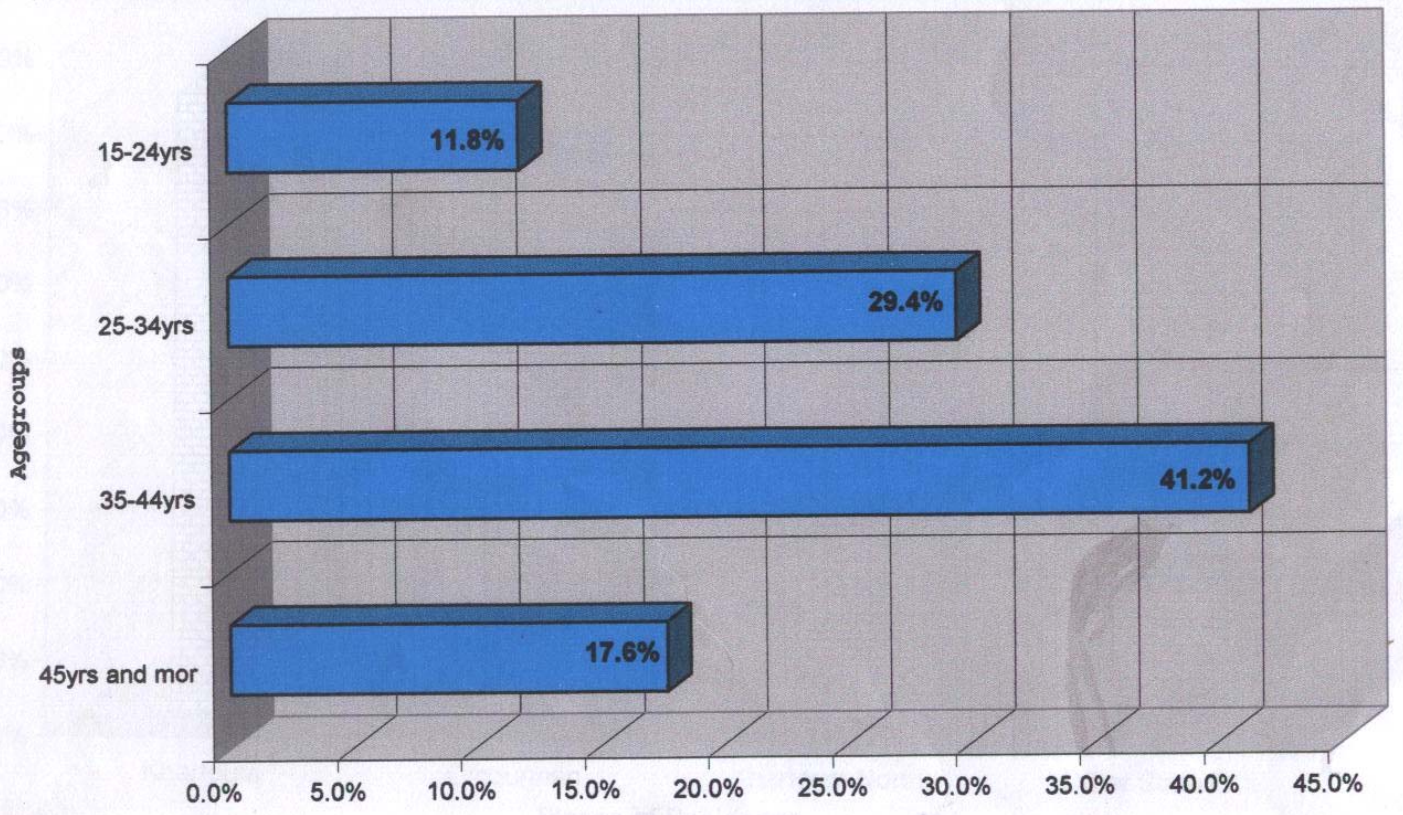


Figure3
Residnce Distribution in patients with Graves' Disease

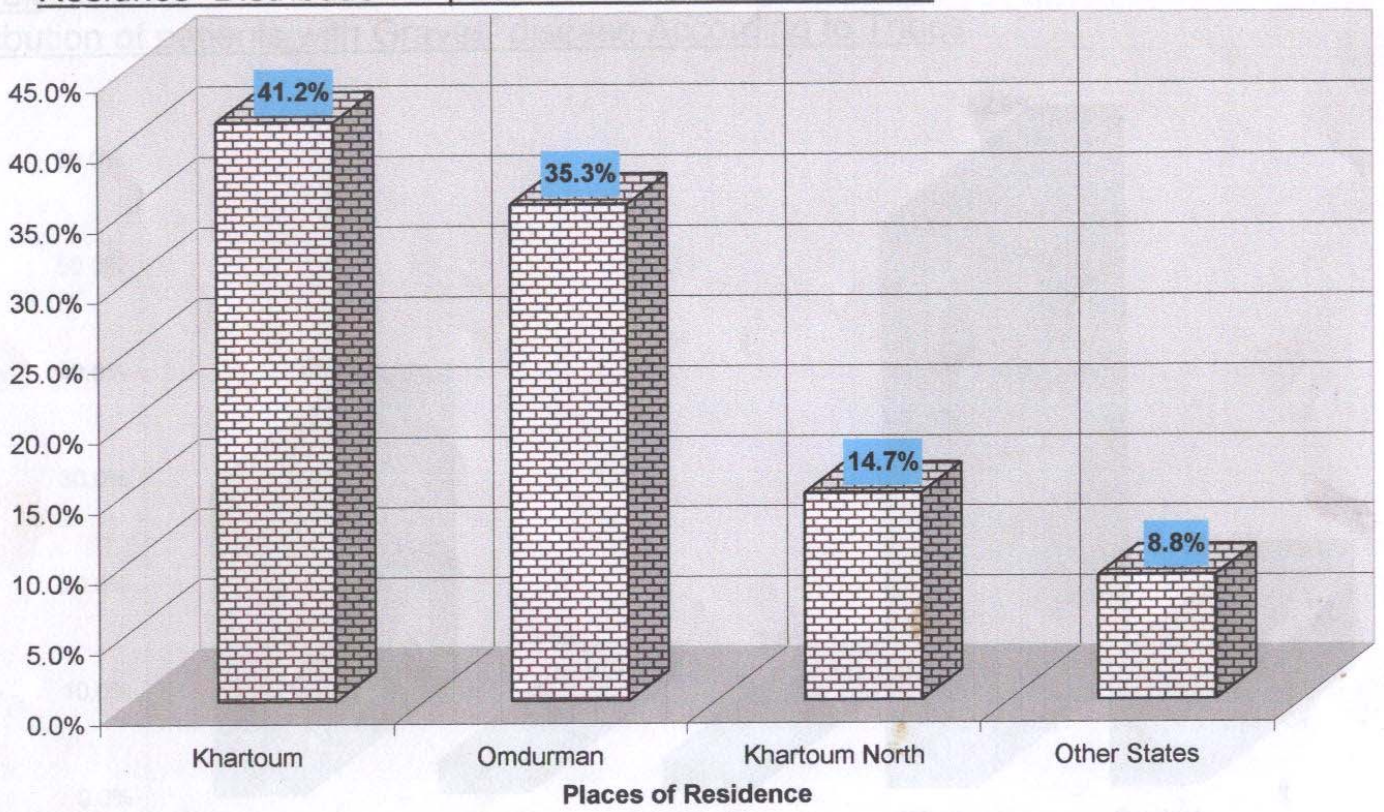
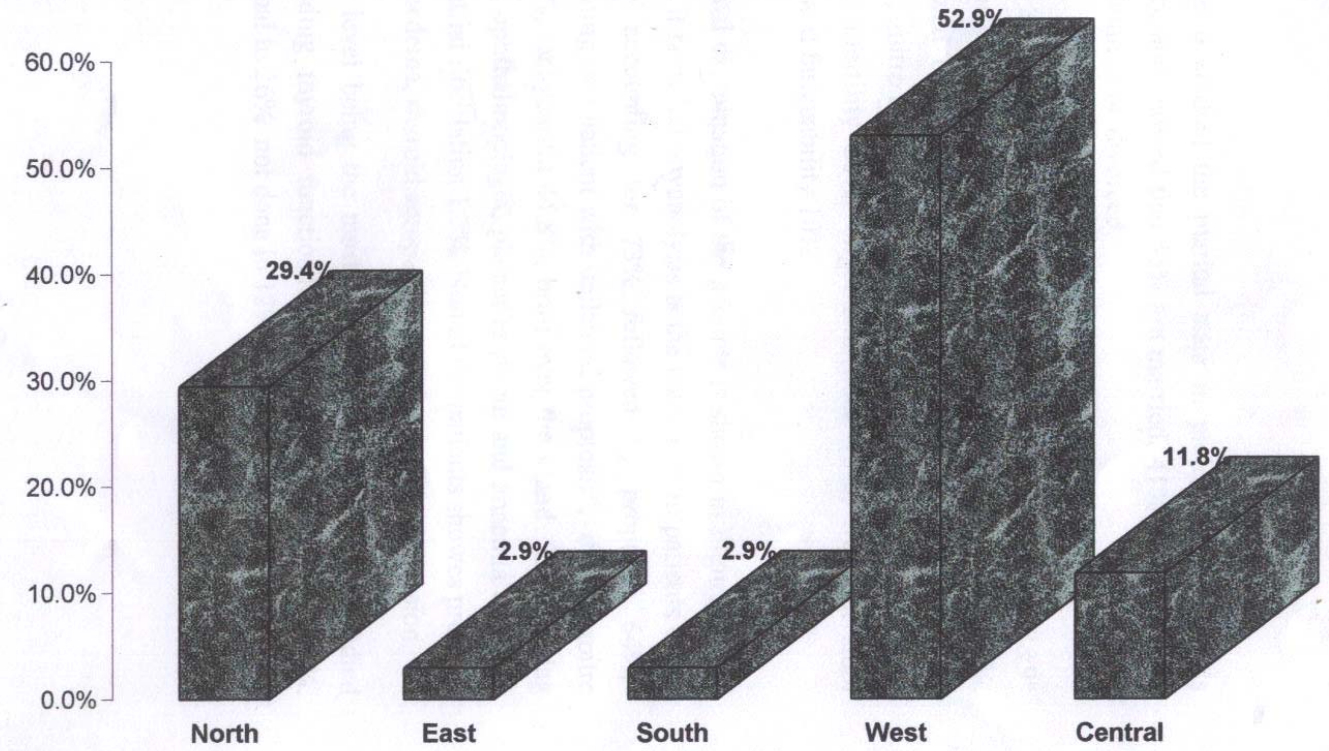


Figure4
Distribution of patients with Graves' disease According to Tribes



• Figure 6 studied the marital state in patients with Grave's disease and showed that 56% are married, 41% are single and 3% found to be divorced.

• Main Symptoms of the patients were shown in Figures:"7,8&9" it showed dislike to hot weather is a major complaints in 70%, followed by irritability and palpitation each accounting for 35% , goitre in 30% sweating in 25%,tremor 24%. Weight loss 23%, infertility 20%, oligomenorrhoea 15%, frequent stool 13% and fatiguability 10%.

• Clinical examination of the patients is shown in Figures 10,11 &12, it revealed onycholysis is the main sign in patients under study accounting for 73% followed by proptosis 64%," including one patient with unilateral proptosis", diffuse goitre 53.4%, tachycardia 44.8%, bruit over the gland 29%, lid lag 13%, ophthalmoplegia, plamer enythem and anaemia each 7% and atrial fibrillation 1.7%. Non of the patients showes pretibial myxoedema, thyroid acropachy or optic nerve compression.

• TSH level being the most important hormone to be studied regarding thyroid functions was found to be low in 62%. Normal in 26% not done in 12% ."Figurel3"

• T_3 level was found to be high in 82% of patients. “Figure 14”.

• T_4 level was found to be high in 79% of patients. “Figure 15”.

• Figure 16 discussed the mode of treatment taken by the patients under study and it shows 58.8% of patients taking antithyroid, 50% taking Beta blockers, only 2.9% underwent radioactive iodine therapy, none of the patients undergone surgery.

Figure5

Distribution of patients with Graves' disease According to Socio-economic Status

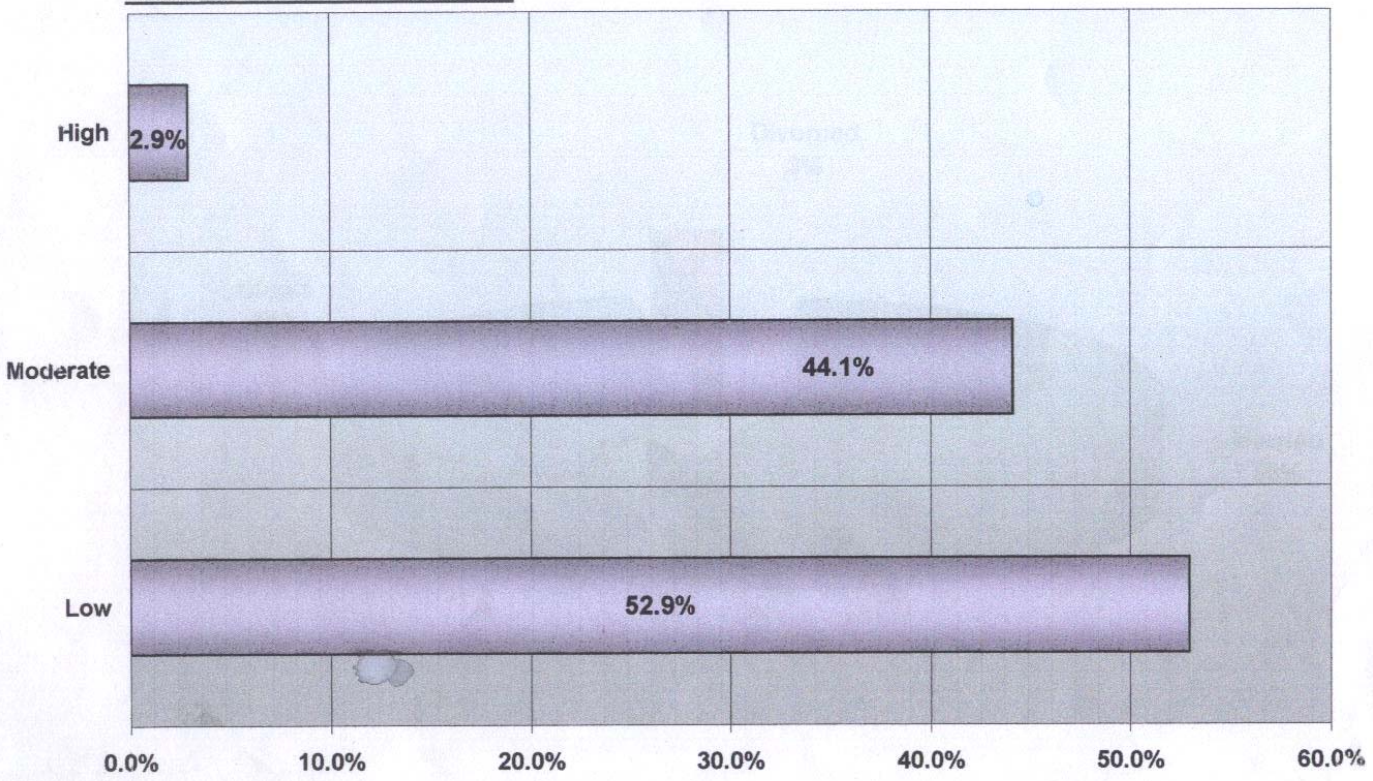


Figure6
Marital status Distribution in patients with Graves' Disease

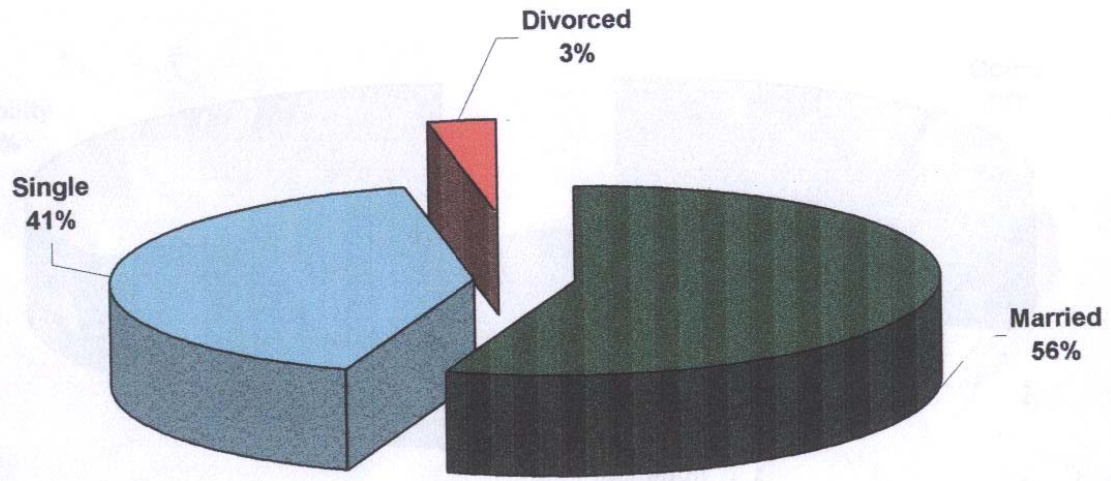


Figure7
Main Symptoms Distribution in
Patients with Graves' Disease

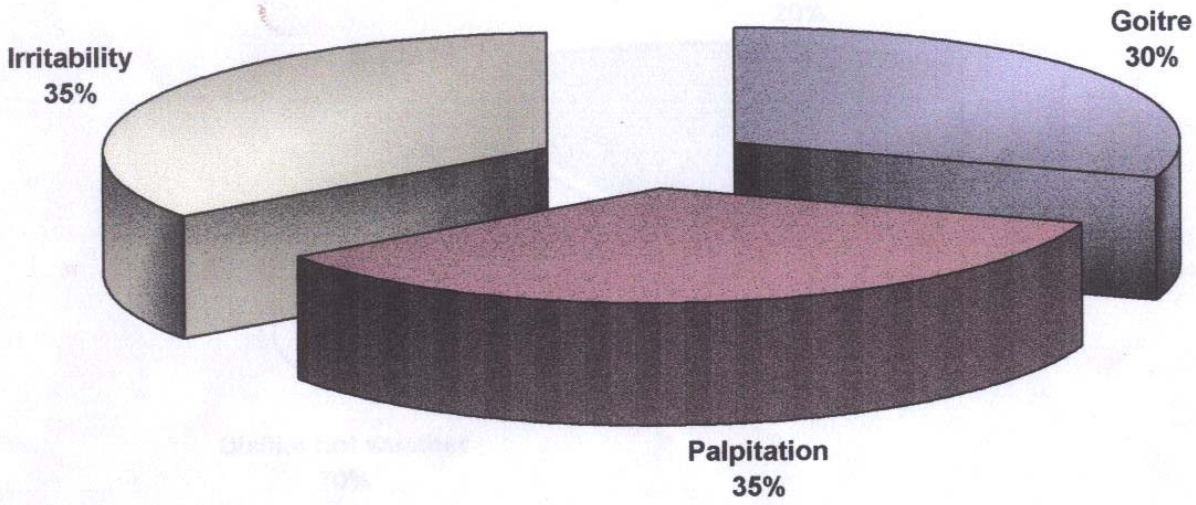


Figure8
Main Symptoms Distribution in Patients with Graves' Disease

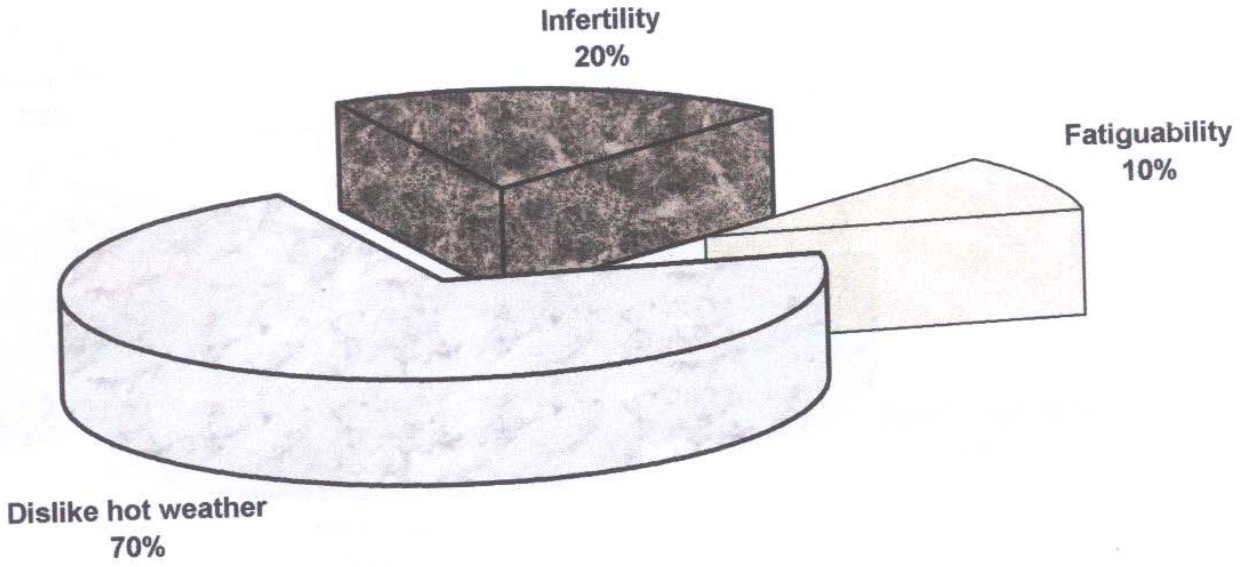


Figure9
Main Symptom Distribution in patients with Graves' disease

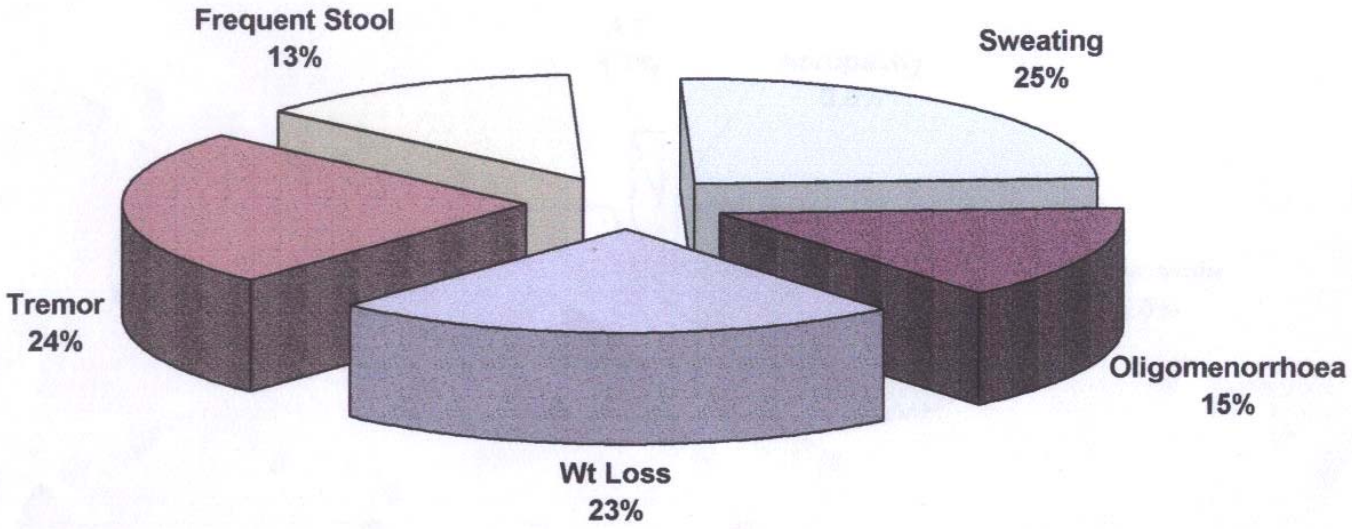


Figure10
Signs Distribution in patients with Graves' disease [1]

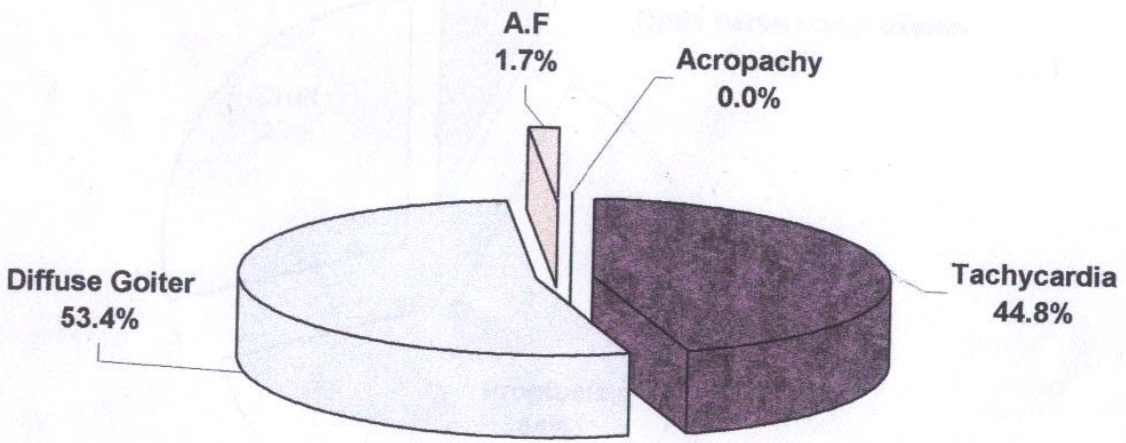


Figure11

Signs Distribution in patients with Graves' disease [2]

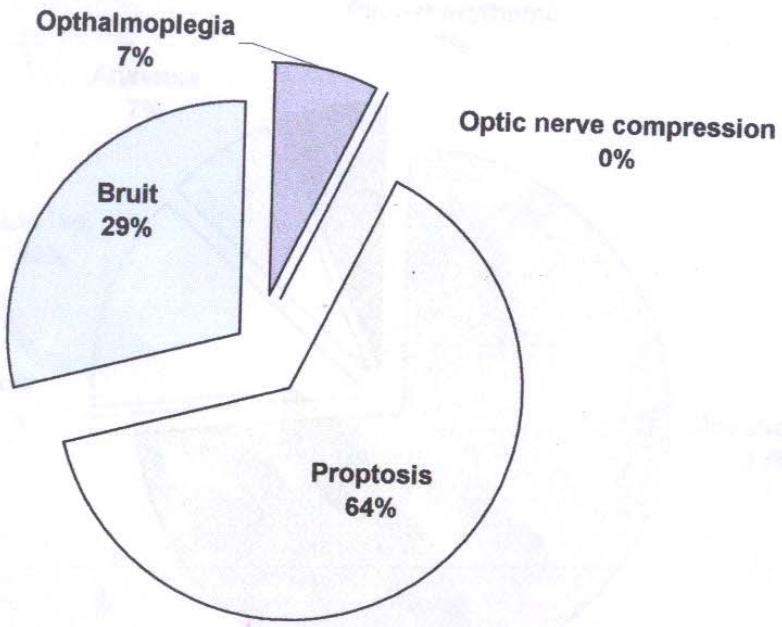


Figure12
Signs Distribution in patients with Graves' disease [3]

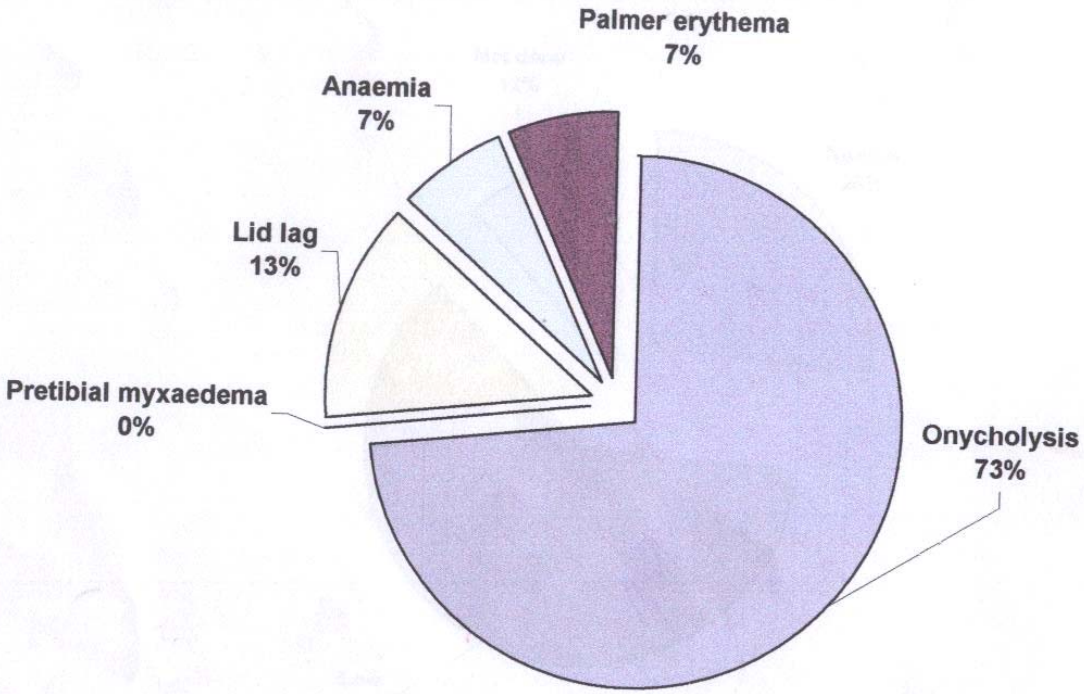


Figure14
T3 Distribution in patients with Graves' disease

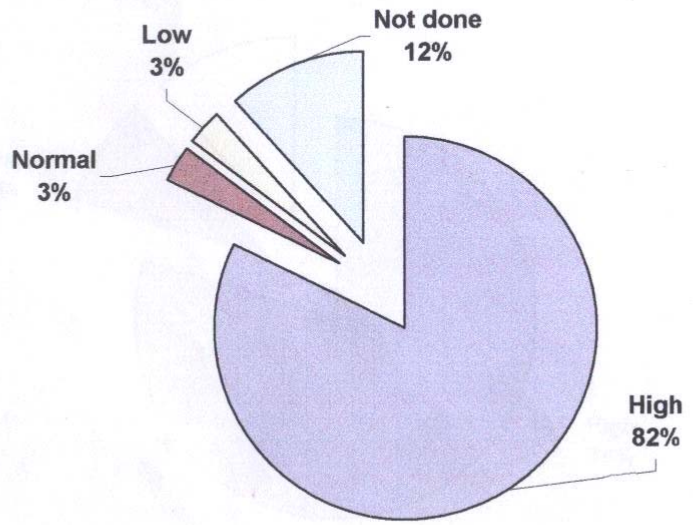


Figure15
T4 Distribution in patients with Graves' disease

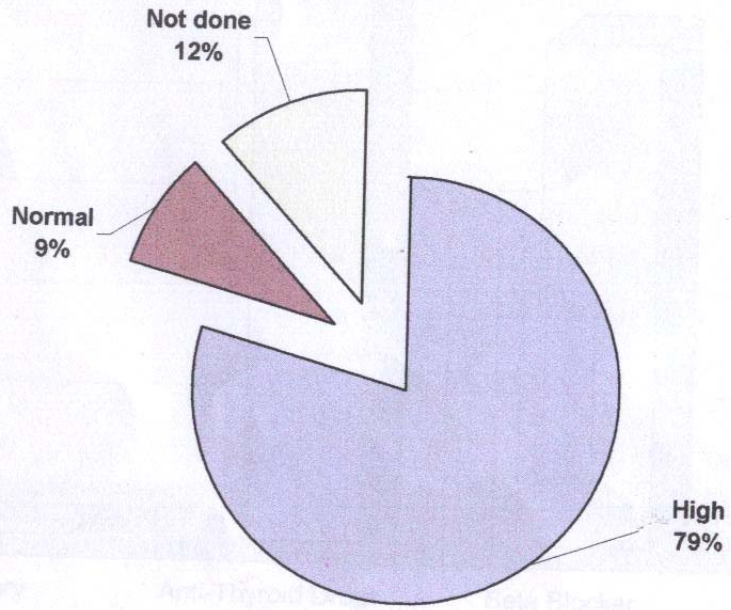
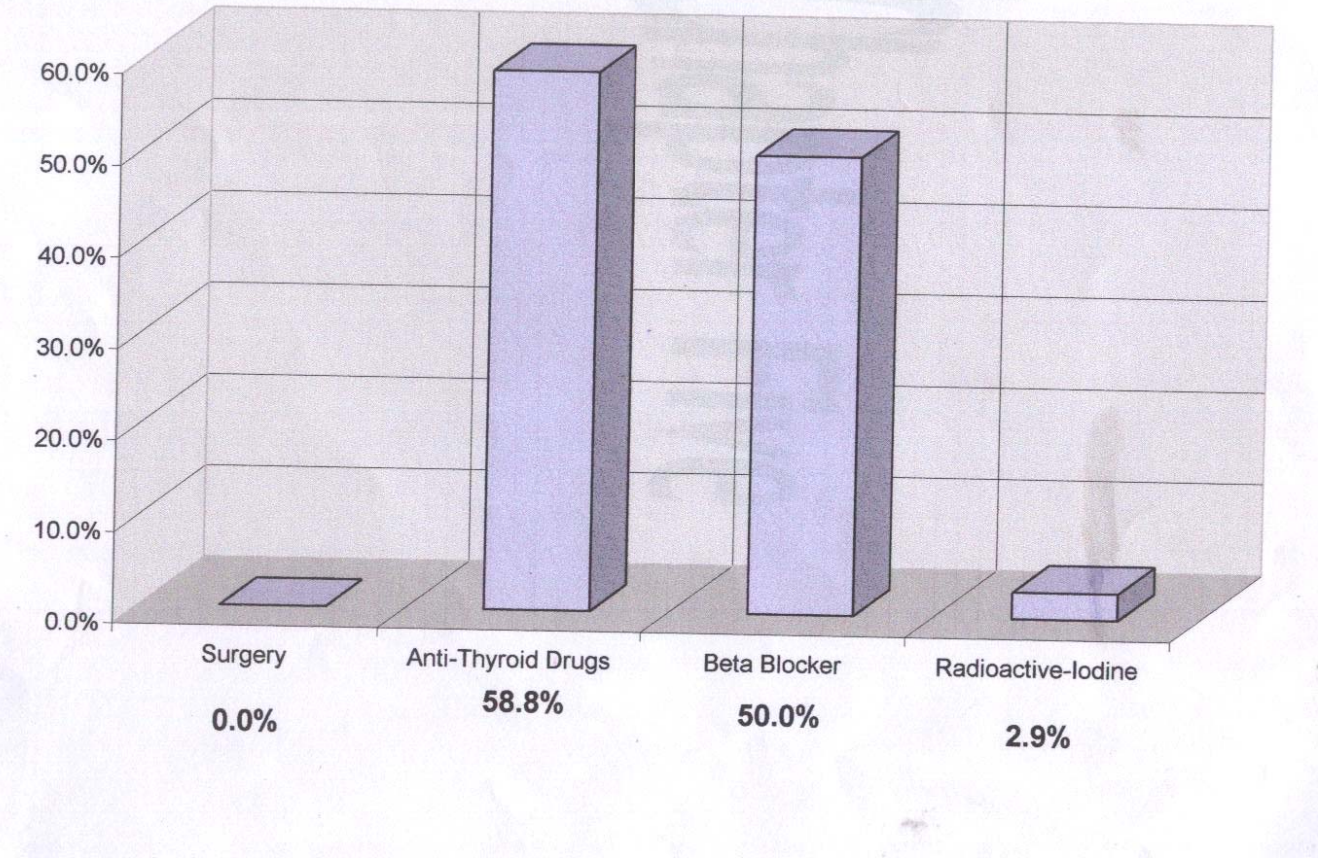


Figure16
Distribution of Mode of Treatment in patients with Graves' disease



DISCUSSION

- The frequency of Graves' disease obtained by detection of TSI, is found to be 69.4%, showing Graves' disease to be the commonest cause of hyperthyroidism in the thyrotoxic patients of K.T.H, this is actually comparable with the international frequency of Graves' disease 60-90%, according to Wick ham's study in the United Kingdom the incidence was reported as 100-200 cases per 100,000 population per year. Another study in U.S in Minnesota estimated incidence to be approximately 30 cases per 100,000 person per year. Our study also agrees with Yagi's [et al, who reported Graves disease in 18.52% out of 23.77% thyrotoxic. Their study depended on the clinical findings to diagnose Graves' disease.
- Most of the patients in this study were residing in Khartoum (41.2%), Omdurman 35.3%. This actually agrees with Kambal's study, 1967 in which he showed Khartoum area to be endemic for Goitre. Another observation is that the big hospitals are found in these areas within an easy reach of the patients, this would possibly explain their crowding in these areas.
- Most of the patients with Graves' disease in this study were from western tribes, this is also found to be in line with Kambal's[29] et al (1952) who showed Darfur Province in the western region to be endemic for Goitre. Woodman's[30] et al (1952) also described Darfur area as endemic for Goitre.
- The females to males ratio was 5-6:1 which showed female domination but the ratio is less than that mentioned in the literature (7-8:1). Yasir's[31] et al found the ratio to be 6.5.%. This reduced

ratio in our study could be attributed to the small number of the study population.

- The mean age group affected in our study was found to be 35- 44 years, which is in line with the literature where the range is 20-40 years.
- The study showed the main symptoms of the patients studied were irritability (3 5%), palpitation 35%, tremor 24%, Yasir's study[31], showed tremors in 76.2% of patients. This smaller figure in our study could be explained by the fact that Yasir's et al included patient who didn't start treatment whereas in our study we have included patients who are already on treatment. These symptoms are mentioned in the literature to be frequent symptoms.
- Other major complaint in our patient was dislike to hot weather (70%), which is mentioned in the literature to be a less common complaint[10]. This could be explained by the fact that our country's climate is hot most months of the year, which adds to their symptomatology.
- Other symptoms in our study were found to be infertility (20%) , fatigability (10%) and frequent stool (13%) not common in our patients which is also similar to the literature.
- The main clinical signs found in our patient were onycholysis (73%). This is actually different from the literature in which it is mentioned to be a less common feature of Graves' disease[1].
- Proptosis in our study was found in 64% of patients with Graves disease, this is comparable with Randeva[32]. et al, who prescribed the condition 60% of cases.

- Tachycardia is a major sign in our study group (44%) which is similar to the literature Atria1 found only in 1 7% of our study group (44%) which is similar at the literature. Atrial fibrillation was dound only in 1.7% of our patients.
- Diffuse Goitre was found in 30% of patients in our study which is different from Randeva[32] et al who prescribed the condition in 90% of patients.
- Palmer erythema as a clinical finding in Graves' disease was evident in 7% of our patients, Anaemia was found in 7% of patients.
- None of our patients showed optic nerve compression. This also agrees with the literature in which signs are mentioned to be rare.
- Thyroid acropachy was not detected in any of our patients, this is actually near to Randeva et al[32], who prescribed the condition in less than 1% of patients.
- Albrights' et al[33] did not mention acropachy as a sign in the guide lines for the diagnosis of thyroid disorders.
- None of the patients in this study was found to have pretibial myxo edema, Yasirs'[31] showed the condition in about .2.4% of patients, which mean that it is a rare clinical finding.
- TSH was found to be low in 62% of patients, normal in 26% of patients and not done in 12% of patients . Theses unexpected findings of normal TSH could be explained by the fact that some of the patients are already on treatment and the results are those taken during their follow-up.
- The study also showed most of the patients (58.8%) taking medical treatment. Only 2.9% received radioactive therapy and none of the

patients undergone surgery. Aibright et al declared that radioactive therapy is the treatment of choice in Grave's disease. He also mentioned that thyroidectomy is rarely performed in patients with Graves' disease in the US.

- Internationally the radioactive therapy is becoming the corner-stone in management of thyrotoxicosis for all ages.

CONCLUSIONS

- Grave's disease is the commonest cause of hyperthyroidism in patients with thyrotoxicosis in the Khartoum Teaching Hospital.
- TSI detection in the sera of patients with hyperthyroidism is crucial to diagnosis of Graves' disease.
- Dislike to hot weather and palpitation are major complaints of patients with Grave's disease.
- Proptosis is a major sign in patients with Graves' disease.
- Onycholysis is common in patients with Graves disease.
- Pretibial myxaedema and thyroid acropachy, although are unique to Graves' disease, both are rare clinical findings.

RECOMMENDATIONS

- High clinical suspicion is needed for diagnosis of Graves' disease due to its wide variations in the clinical patterns.
- Accurate diagnosis of Graves' disease should be achieved by detection of thyroid stimulating immunoglobulins (TSI) in the patient serum using the radioimmunoassay assay (RIA).
- Field studies are needed regarding thyroid diseases especially in Western Sudan in order to prevent late presentation and major complications.
- More studies are awaited in the evaluation of radioactive iodine therapy in Sudan, so as to extend its use in the management of Graves' disease.

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Questionnaire

File No: ☐ Serial No: ☐

Sex: ☐ Age: ☐

Residence: ☐ Occupation: ☐

Marital Status: ☐ Tribe: ☐

Socio—economic status: Low ☐ Moderate ☐ High ☐

Duration of Thyroid disease:

Symptoms at presentation:

- Wt Loss ☐ - Goitre ☐
- Tremors ☐ - Palpitation ☐
- Frequent stool ☐ - Irritability ☐
- Sweating ☐ - Dislike to hot weather ☐
- Oligomenorrhoea ☐ - Infertility ☐
- Others……

Signs:

- Tachycardia ☐ - Proptosis ☐
- Goitre ☐ - Bruit over the gland ☐
- A.F. ☐ - Onycholysis ☐
- Acropachy ☐ - Pretibial Myxaedema ☐
- Ophthalmoplegia ☐ - Lidlag ☐
- Optic nerve compression ☐ - Anaemia ☐

☐

- Others

Last Lab investigate:

TSH ☐

T3 ☐

T4 ☐

TSI ☐

Has the patient received treatment Yes ☐ No ☐

- If yes specify
- Beta blocker
- Anti- thyroid drugs
- Radioactive- iodine
- Surgery